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Collapsing glomerulopathy: beyond serendipity in mouse genetics

Peter J. Nelson[1] and Leslie A. Bruggeman[2]

Clinical correlates suggest that collapsing glomerulopathy results from the pathogenic interaction between patients' intractable genetic susceptibilities and environmental insults. When the environmental insults include a virus that introduces its own pathogenic genes, the interactions become more complex. Chan *et al.* combine reverse and forward genetic techniques in mice toward understanding this complexity with HIV and identify candidate genetic modifiers of collapsing glomerulopathy.

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Many parenchymal renal diseases characterized by podocyte injury result from the interaction of genetic and environmental factors.[1] Collapsing glomerulopathy (CG) is no exception. Since its first clinical-pathologic descriptions almost three decades ago, two general clinical correlates suggesting causality for CG continue to be strengthened: its predilection for patients of African descent; and its occurrence in conditions—many environmentally derived—with preceding immune activation, particularly T-helper type 1 (Th1)-polarizing disorders.[2] Experimental evidence that the genetic susceptibilities of the former may be unmasked by the latter is only now forthcoming.

In this vein, a new study by Chan *et al.*[3] (this issue) makes an exciting advancement toward understanding genetic susceptibilities for CG. The success of their multistep approach starts historically with the often serendipitous outcomes of reverse genetics in mice. In the late 1980s, the laboratories of Malcolm Martin and Abner Notkins at the US National Institutes of Health collaboratively used transgenic technology to create FVB/N-strain mice bearing subgenomic human immunodeficiency virus-1 (HIV-1) proviral transgenes in efforts toward a rodent model of AIDS. Although human AIDS-like immunodeficiency was not observed in the many transgenic founders produced, a few curiously and unexpectedly developed renal disease strikingly similar to CG in HIV-infected patients.[4]

Using the FVB/N Tg26 line resulting from this early discovery,[4] forward genetic techniques were then employed to map genetic susceptibility loci for CG.[5] Cross-breeding of FVB/N Tg26 mice with several different inbred strains of mice showed a considerable strain-dependent variation in the severity of CG in F_1 progeny. To identify genetic susceptibility loci present in one such strain, CAST, a mouse genome-wide analysis of linkage to increased severity of CG, was performed on B_1 progeny from backcrossing of (FVB/N Tg26×CAST)F_1 with FVB/N Tg26 mice. This mapped a genetic susceptibility locus, termed *HIVAN1*, to CAST mouse chromosome 3A1–A3.

[1]*Division of Nephrology, New York University School of Medicine, New York, NY, USA;* [2]*Department of Medicine and Rammelkamp Center for Education and Research, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA*
Correspondence: *Peter J. Nelson, Division of Nephrology, Smilow Research Center, New York University School of Medicine, 522 First Avenue, New York, NY 10016, USA.*
E-mail: peter.nelson2@nyumc.org

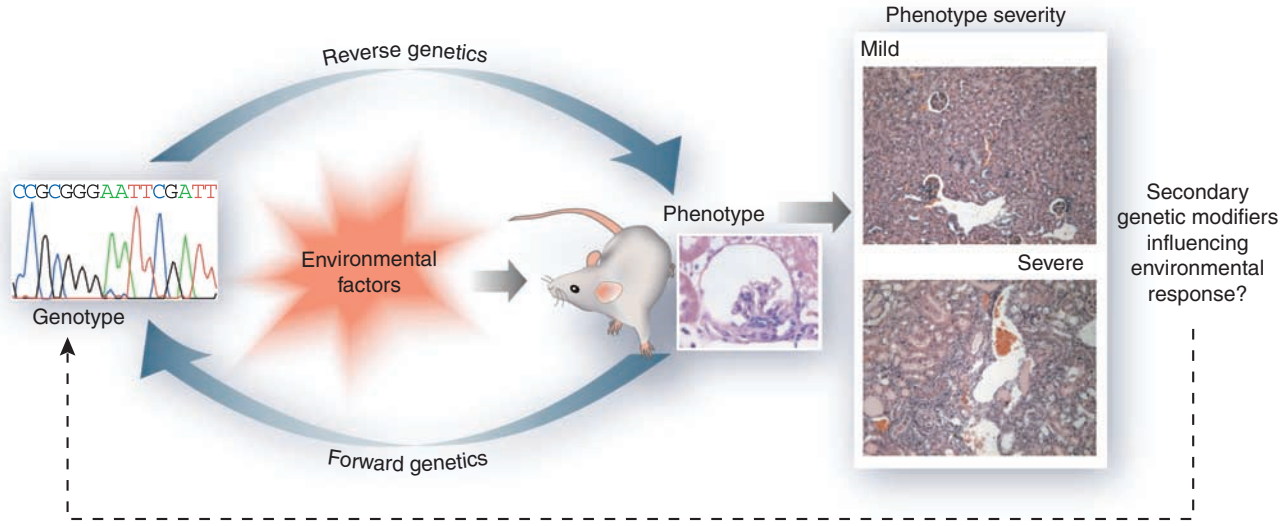

Figure 1 | The interplay of forward and reverse genetics in identifying genetic susceptibilities for collapsing glomerulopathy. Environmental factors may unmask genetic susceptibilities to influence the onset or progression of collapsing glomerulopathy. (Histopathology images adapted from ref. 9 with permission.)

Now, Chan *et al.* again combine reverse and forward genetic techniques to provide confirmatory evidence that *HIVAN1* likely contains genetic modifiers of CG.[3] Starting with the B_1 progeny noted above, backcrossing with FVB/N mice was continued another nine times to retain and passage *HIVAN1* from the CAST strain while at the same time enriching for the FVB/N genetic background. Clinical analyses of subsequent intercrosses with FVB/N Tg26 mice showed that those Tg26 progeny bred congenic for *HIVAN1* had significantly earlier onset and severity of CG when compared with those lacking *HIVAN1*. Then, using FVB/N mice congenic for *HIVAN1* for meiotic mapping and linkage to increased severity of CG, *HIVAN1* was further refined to an interval containing 126 candidate susceptibility genes. Of those annotated, 22 contain single-nucleotide polymorphisms that differ between the FVB/N and CAST strains, already offering candidate genetic modifiers for future study.

This multistep approach of combining forward and reverse genetics toward identifying and confirming susceptibility genes was recently successful in another model of CG. Discovered serendipitously by Mary Lyon over 3 decades ago,[6] CS7BL/6 kd/kd mice are susceptible to CG due to a genetically acquired mitochondriopathy.[7] Mapping through forward genetics showed the genetic lesion in this model to be a missense mutation in the *Pdss2* gene, encoding an enzyme required for mitochondrial coenzyme Q biosynthesis; subsequent reverse genetics to develop targeted cell-specific mutants demonstrated that loss of *Pdss2* in podocytes alone determined the susceptibility for CG.[8] The requirement of environmental factors to unmask this susceptibility was discovered when germ-free but not specific-pathogen-free *kd/kd* mice were found to be protected from developing CG.[9] Intriguingly, under germ-free conditions, commensals needed for homeostatic Th1 development are absent, resulting in default systemic Th2 skewing;[10] this lends credence to the clinical correlate suggesting that Th1 states, even 'clinically silent' ones, may precipitate CG in susceptible patients.[2]

Interrogation of how environmental factors and the candidate genetic modifiers of CG identified by Chan *et al.*[3] play a pathogenic role in the setting of HIV infection, however, is likely to be more complex (Figure 1). For example, the infected host cell's environment markedly influences infection with HIV and whether HIV enters latency or becomes transcriptionally active,[11] and host genetic modifiers might alter environmentally induced changes in the HIV life cycle. During productive infection, HIV gene products can co-opt and hijack host molecular pathways controlling proliferation, apoptosis, and inflammation,[12] and host genetic modifiers may synergistically activate or amplify these pathways. Alternatively, host genetic modifiers may act sequentially before or after any pathogenic role of HIV to precipitate or accelerate CG. Indeed, any of these and many other combinations of possibilities exist, and deciphering it all may require a more systems-biology approach to host–pathogen interactions.[13] In any respect, research into the genetic susceptibilities for CG is moving beyond serendipity, and the time-consuming approach of Chan *et al.*[3] that is needed to provide answers is noteworthy.

DISCLOSURE

The authors declared no competing interests.

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Lanthanum and phosphate: science, policy, and survival

Alastair J. Hutchison[1]

Mineral metabolism in chronic kidney disease is attracting intense interest and unprecedented levels of research. The pharmaceutical industry has responded by developing various new agents. Bervoets *et al.* report the use of an unusual combination of basic-science techniques to increase understanding of the kinetics of one such agent—lanthanum carbonate—in the gastrointestinal tract and liver. However, do we need to answer more fundamental clinical questions before we can definitively identify the role of similar new and expensive drugs?

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Ten years ago, mineral metabolism in dialysis patients was of limited interest to the nephrology community, perhaps because the effect of its derangement was thought to be similarly limited—to the skeleton. However, cardiac and cerebral vascular disease is responsible for the majority of deaths in patients with chronic kidney disease, and deposition of phosphate and calcium can be seen radiologically in the blood vessels of many dialysis patients. We know that the 5–year survival of patients around the age of 60 years and on dialysis is worse than that of patients with breast cancer and colon cancer, and only marginally better than that of patients with ovarian cancer (Table 1).

[1]*Manchester Institute of Nephrology and Transplantation, The Royal Infirmary, Manchester, UK*
Correspondence: *Alastair J. Hutchison, Renal Dialysis Unit, The Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK.*
E-mail: ajh@nephrologist.co.uk

Hence, reports published in 1998 of an association between serum phosphate levels and mortality based on data from the United States Renal Data System[1] resulted in an explosion of interest and research. Despite an almost complete absence of confirmatory data from interventional randomized controlled trials, the link seemed to fit intuitively in the minds of most clinicians, and as a result the quest for the 'ideal phosphate binder' has accelerated in a way that would never have been envisaged a decade ago. Lanthanum carbonate is a product of this quest, but because previously it had been thought to have no medicinal applications, very little was known of its pharmacokinetics, and reasonable concerns have been raised about possible deposition and mechanisms of elimination. Sadly, these concerns have been amplified by the marketing strategies of other phosphate binder manufacturers, so that the injection of some elegant science into the debate is both timely and welcome.

Bervoets *et al.*[2] (this issue) demonstrate masterly use of advanced basic-science techniques to investigate and clarify a clinical conundrum. A combination of three techniques, probably not familiar to most nephrologists, was used to localize lanthanum to the lysosomes in the liver of rats. First lanthanum was co-mapped with iron with the synchrotron particle accelerator in Grenoble to induce X-ray microfluorescence; then transmission electron microscopy and finally electron energy-loss spectroscopy enabled identification and subcellular localization of lanthanum to the lysosomes.

Lysosomes are organelles generated by the Golgi apparatus that appear in the cytoplasm as bodies bounded by a single membrane. They can contain over 30 different hydrolytic enzymes, and material requiring digestion is first deposited within them. In addition, they can take up antigens and metals, including copper and iron. This study appears to have also identified the liver lysosomes as the route of transport for lanthanum, from serum to bile and, thereafter, excretion via the intestine. The other particularly intriguing aspect of this study is the demonstration that intestinal uptake of lanthanum appears to be increased in rats with chronic kidney disease compared to those with normal kidney function. The difference is relatively small but leads the authors to speculate that it may be related to increased intestinal 'permeability,' which has previously been demonstrated in uremic rats. The mechanism by which intestinal permeability may be increased is not known, but Bervoets *et al.*[2] focus on the possibility that it is related to an inflammatory state. However, it is also known that both zinc deficiency[3] and hyperprolactinemia,[4] neither of which is uncommon in patients on dialysis, modulate intestinal permeability, and there may also be other mechanisms at play.

Intestinal transporters of dietary 'essential metals,' including zinc transporters, divalent metal transporter 1 (DMT1), ferroportin, and calcium transporter 1, have been identified in mammals. These transporters are upregulated or downregulated according to the host's essential-metal nutritional status. For example, iron depletion is thought to upregulate mRNA encoding functional DMT1, an apical iron